

## II. REMARKS

The non-final Office Action dated February 5, 2007, has been received and carefully noted. The above amendments and the following remarks are being submitted as a full and complete response thereto.

Claims 1, 7-22, 24, 32, 34, 35, and 39-45 are pending. Claims 32, 34, and 35 are withdrawn. Claims 1, 9, and 40 are amended and claims 6, 26, and 46-49 are canceled. Applicants reserve the right to file one or more divisional applications to the cancelled subject matter. The amendments are supported by the originally filed specification and claims. In particular, claim 1 is amended to be directed to elected subject matter and claim 9 is amended to correct a typographical error, as requested by the Examiner. Meanwhile, the amendments to claim 40 are supported by Example 1 of the specification. No new matter is added.

The specification is objected to for not containing a brief description of the drawings. This objection is traversed.

Applicants respectfully submit that the specification includes a "Brief description of the drawing" section on page 35. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection to the specification.

Claims 1, 6-22, 24, and 29-48 are objected to for containing elected and non-elected subject matter. Applicants respectfully submit that this rejection is overcome by the above amendments to claim 1 and the cancellation of claims 6 and 46-48. Accordingly, Applicants respectfully request withdrawal of the objection to claims 1, 6-22, 24, and 29-48.

Claim 9 is objected to for containing a typographical error. Applicants respectfully submit that this objection is overcome by the above amendment to claim 9, inserting a comma between the term "perchloric acid" and the term "polystyrene sulphonic acids," as requested by the Examiner. Accordingly, Applicants respectfully request withdrawal of the objection to claim 9.

Claims 40 and 41 are rejected under 35 U.S.C. § 112, first paragraph, for insufficient written description. This rejection is traversed.

Applicants respectfully note that present claim 40 is directed to "[a] process according to claim 1, wherein Y-NO<sub>3</sub> of step (3) is sodium nitrate and tetrabutylammonium nitrate, the third solvent is a mixture of butyl acetate and acetonitrile, and step (3) is conducted at a temperature of 87°C." Meanwhile, Example 1 of the present specification discloses the following paragraph:

2-[2-(Nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IVa).

The mesylate IIIa (608.8 g, 1.317 mol) and tetrabutylammonium nitrate (120.8 g, 0.397 mol) were mixed with n-butyl acetate (1.7 L) at 60°C. Acetonitrile (0.70 L) and sodium nitrate (459.7 g, 6.668 mol) were added at 60°C. and the resulting slurry was agitated at a jacket temperature of 87°C. for 50 h. Water (2.4 L) was added and the jacket temperature was lowered to 50°C. After 10 min of stirring the water phase was separated off and the organic phase was washed twice with water (2x2.4 L) at 50°C. The organic phase was then evaporated down to a volume of 1.5 L. Isopropanol (3.1 L) was added at 50°C. and the resulting solution was cooled to an inner temperature of -12° C. over 15 h. After 7 h of stirring at -12°C. the formed crystals were filtered off and washed with isopropanol (0.84 L) and then dried under vacuum at 40°C., to give 527.7 g (93.4%) of pure IVa. The purity according to HPLC was >99 area-%.

(specification, page 38, lines 13-25) (emphasis added). As such, Example 1 discloses the reactants and temperature of 87°C of claim 40.

Meanwhile, claim 41 is directed to “[a] process according to claim 1, wherein Y-NO<sub>3</sub> of step (3) is sodium nitrate and tetrabutylammonium nitrate, the third solvent is a mixture of n-butyl acetate and water, and step (3) is conducted at a temperature of 90°C.”

Example 1 of the present specification discloses the following paragraph:

2-[2-(Nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IVa).

The mesylate IIIa (471 g, 1.02 mol) was mixed with n-butyl acetate (1.9 L) at 60°C. Tetrabutylammonium nitrate (62.3 g, 0.204 mol) and sodium nitrate (355 g, 5.15 mol), both ground using a mortar, were added at 60°C. and the resulting slurry was agitated at a jacket temperature of 60° C. for 10 min. Water (45.9 mL) was added and the jacket temperature was raised to 85°C. After 16 h 30 min of vigorous stirring the jacket temperature was raised to 90°C. and after a total of 51 h the mixture was cooled to 50°C. Water (1.9 L) was added and the resulting twophase system was stirred at 50°C. for 5 min. The water phase was separated off and the organic phase was washed twice with water (2x1.9 L) at 50°C. The organic phase was then evaporated down to a volume of 1.0 L. Isopropanol (2.36 L) was added at 50°C. and the resulting solution was cooled to an inner temperature of -11°C. over 15 h. The formed crystals were filtered off and washed with isopropanol (1.0 L) and then dried under vacuum at 40°C., to give 361.6 g (82.7%) of pure IVa. The purity according to HPLC was 98 area-%.

(specification, page 37, line 31 to page 38, line 11) (emphasis added). As such, Example 1 also discloses the temperature of 90°C and the reactants of claim 41.

As such, Applicants respectfully submit that the specification provides sufficient written description for the temperatures of reaction of claims 40 and 41. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 40 and 41 under 35 U.S.C. § 112, first paragraph, for insufficient written description.

Claims 1, 6-22, 24, and 39-48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Del Soldato et al. (WO 95/30641) in view of Lai et al. (U.S. Patent No. 6,355,666), Cainelli et al. (J. Chem. Soc. Perkin. Trans. (1987) 2637-2642) and Hwu et al. (Synthesis (1994) 471-474). This rejection is traversed.

Applicants agree with the Examiner that "Del Soldato et al. does not teach the reaction of diclofenac with a glycol linker, the reaction of that product with an alkylsulfonyl source, or reaction with an alkali nitrate. Also, the exact details of the solvent, purification, and other parameters provided in dependent claims are not addressed" (Office Action, page 6). However, Applicants respectfully submit that Lai et al., Cainelli et al., and Hwu et al., alone or in combination, do not satisfy the deficiencies of Del Soldato et al.

In particular, Applicants respectfully submit that none of the cited references teach or suggest conversion of a sulfonate intermediate that is a mesylate derivative "at a maximum temperature of 90°C" as in step (3) of present claim 1, much less that it is possible to convert the mesylate derivatives in high yield at such a low temperature (see, for example, the 93.4% purity of the compound of formula IVa of Example 1 on page 38). In contrast, Hwu et al. and Cainelli et al. teach away from the claimed temperature. Hwu et al. discloses the conversion of benzenesulfonate to the corresponding nitrate by tetrabutylammonium at a temperature from 110-135°C. See, e.g., Hwu et al.'s disclosure of a "new and cost-effective method ... developed for the preparation of nitrate esters ... at 110-135°C" (Hwu et al., page 471, left column, first paragraph and the Table on page 471). Meanwhile, Cainelli et al. discloses conversion of mesylate derivatives to the

correspondent nitrates by treatment with tetrabutylammonium nitrate in toluene at reflux (i.e., at toluene's boiling point of 110°C) (Cainelli et al., page 2640, left column, third full paragraph, and page 2641, left column, fourth full paragraph). Meanwhile, Lai et al. merely discloses the preparation of a sulfonate intermediate and does not teach or suggest conversion of the sulfonate derivative to a NO-donating compound, much less at the low temperature of the presently claimed invention.

Applicants submit that carrying out the nitration reaction at the low temperatures of the presently claimed invention allows those of skill in the art to obtain the final product with high chemical yields while avoiding expensive and difficult purification processes for obtaining the product with an acceptable pharmaceutical purity.

Further, Applicants note that this rejection has been rendered moot in part by the above cancellation of claims 6 and 46-48.


As none of the cited references, alone or in combination, teach or suggest all of the elements of the presently claimed invention, Applicants submit that the presently claimed invention would not have been obvious to those of skill in the art, much less the unexpected advantages thereof. Accordingly, for at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 6-22, 24, and 39-48 under 35 U.S.C. § 103(a) over Del Soldato et al. in view of Lai et al., Cainelli et al. and Hwu et al.

### III. Conclusion

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event that this paper is not being timely filed, the Applicants respectfully petition for an appropriate extension of time. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account Number 01-2300, referencing Docket Number 026220-00064.

Respectfully submitted,



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